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WHO Expert Committee on Drug Dependence

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Geneva, 22–28 April 1986

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WHO EXPERT COMMITTEE ON DRUG DEPENDENCE

Twenty-third Report

INTRODUCTION

The WHO Expert Committee on Drug Dependence met in Geneva from 22 to 28 April 1986. The meeting was opened on behalf of the Director-General by Dr Lu Rushan, Assistant Director-General, who drew attention to the important work of the Expert Committee in making recommendations for the international control of narcotic drugs and psychotropic substances. Under the terms of the Single Convention on Narcotic Drugs adopted in 1961 and the Convention on Psychotropic Substances adopted in 1971, WHO must pass on the Expert Committee's recommendations to the Secretary-General of the United Nations. This Expert Committee was convened in accordance with the *Guidelines for the WHO Review of Dependence-producing Psychoactive Substances for International Control.*[1] The request for the review of 31 barbiturates by the Expert Committee came from the United Nations Commission on Narcotic Drugs.

Dr Lu Rushan outlined the tasks of the Expert Committee as follows:

(*a*) To make recommendations regarding the need for and level of control of the 31 substances under review;

(*b*) To state its views regarding the way the Expert Committee could report its recommendations for such control;

(*c*) To advise WHO on how it could best fulfil its obligations under the international drug control treaties.

1. GENERAL CONSIDERATIONS

This was the second time that the Expert Committee on Drug Dependence had met since the formulation of the new procedure for

[1] *Executive Board, seventy-seventh session, Geneva, 8–17 January 1986; resolutions and decisions; annexes.* Geneva, 1986 (Annex 9) (unpublished WHO document EB77/1986/REC/1).

WHO review of psychoactive drugs for international control, which was first approved by the WHO Executive Board at its seventy-third session;[1] it was also endorsed and commended by the ninth special session of the United Nations Commission on Narcotic Drugs at its meeting held in February 1986 in Vienna. Since approval by the Executive Board, WHO has modified the guidelines slightly in order to facilitate their practical application. The modifications have covered two areas: (*a*) the attendance at the meetings of the Programme Planning Working Group (PPWG) of non-members of the PPWG; and (*b*) meetings between members of the WHO Expert Committee on Drug Dependence and non-members of the Expert Committee.

As regards the PPWG meeting, the guidelines now state:

> "The United Nations Division of Narcotic Drugs, INCB [International Narcotics Control Board] and Interpol, as well as collaborating centres whose activities are directly relevant to the review procedure, should be invited to send a representative to meetings of PPWG. Representatives of governments and representatives from competent nongovernmental organizations in official relations with WHO or in consultative status with the United Nations Economic and Social Council may be invited to attend a part of the meeting. The nongovernmental organization contingent from the pharmaceutical industry may include representatives of the pharmaceutical industry under the aegis of IFPMA [International Federation of Pharmaceutical Manufacturers Associations] or other interested persons as defined in paragraph 40. Experts or other special advisers or representatives may also be invited for a part of the meeting if the need arises."

All participants are free to express their points of view on any part of the agenda of the PPWG meeting. The outcome of the discussions with non-members is reported to the Expert Committee in an addendum to the critical review document prepared by the WHO Secretariat.[2]

Concerning the meetings of non-members with the members of the Expert Committee on Drug Dependence (ECDD), the guidelines state that representatives of government, competent non-governmental organizations in official relations with WHO, and the pharmaceutical industry "may be invited to have a meeting with the

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[1] *WHO handbook of resolutions and decisions of the World Health Assembly and the Executive Board.* Geneva, World Health Organization, Volume II, 1985, p. 109 (resolution EB73.R11).

[2] Prior to the meeting of the Expert Committee, the WHO Secretariat carries out a detailed assessment of all the drugs to be reviewed by the Committee and compiles all the relevant information in a critical review document; this document is then submitted to the Committee for discussion.

members of the ECDD before the start of the ECDD meeting to present additional information concerning the reviewed substances and to clarify written submissions".

The revised guidelines were approved by the WHO Executive Board at its seventy-seventh session in decision EB77(3).[1] At its third meeting, the Programme Planning Working Group proposed a model report form and this was presented to the present Expert Committee for consideration. In its twenty-second report, the Expert Committee on Drug Dependence[2] presented details of the steps undertaken by the WHO Secretariat in preparing the *Critical review of information on 28 uncontrolled phenthylamines for the 22nd Expert Committee on Drug Dependence*;[3] the same steps were followed in preparing a critical review document for 31 barbiturates reviewed by the present Expert Committee.[4]

1.1 The format of this report

In response to suggestions from the United Nations Commission on Narcotic Drugs and the WHO Executive Board, the PPWG at its third meeting proposed a format for the Expert Committee on Drug Dependence to use in reporting its review of each substance. The Expert Committee agreed to use the new format for the present report, information for each substance reviewed being presented under the headings listed below. The comments under each heading indicate how the information corresponds with that provided in the critical review document.

Substance identification

This corresponds to section 1 (Substance identification) of the critical review and includes the official name (INN), Chemical Abstracts Service (CAS) registry number, chemical name, and other common names of the substance. Also included is the isomeric state of the compound.

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[1] *Executive Board: seventy-seventh session, Geneva, 8–17 January 1986; resolutions, decisions, annexes*. Geneva, 1986 (unpublished WHO document EB77/1986/REC.1).

[2] WHO Technical Report Series, No. 729, 1985.

[3] Unpublished WHO document, MNH/PAD/84.13.

[4] *Critical review of information on 31 uncontrolled barbiturates for consideration of the 23rd Expert Committee on Drug Dependence* (unpublished WHO document MNH/PAD/85.12.Add 1).

Similarity to already scheduled substances

This section includes information from sections 3, 4, and 5 (General pharmacology, Toxicology—including adverse reactions in humans, and Pharmacokinetics) of the critical review in which these aspects of the substance under review are compared with other already scheduled substances. In particular, in this section the Expert Committee has included information relating to the pharmacological classification, ill effects and metabolism of the substance compared with these characteristics of pentobarbital and/or phenobarbital, which are already scheduled under the Convention on Psychotropic Substances. The Expert Committee slightly altered the wording of the PPWG's recommendation as regards the title of this by changing the word "standard" to "already", since they felt this was more compatible with the criteria of the Convention on Psychotropic Substances.

Effects on central nervous system and mental functions

This section corresponds to the relevant parts of section 3 (General pharmacology) of the critical review.

The Expert Committee felt that there was considerable overlap between sections 2 and 3 of the proposed report format.

Dependence potential

In the report format suggested by the PPWG, information from Section 6 (Dependence potential) of the critical review would be included if this information was specific to the drug under review. This information would include experimental studies on physical dependence, drug self-administration (psychic dependence) in animals and man, and experimental studies on subjective effects in man. In addition, case reports on dependence in man would be included.

In the critical review document, although not in the original WHO guidelines, the phrase "abuse liability" was used. Thus, in the critical review, dependence potential and abuse liability were used interchangeably. The terms "dependence", and "dependence potential" have been adequately defined in many WHO

publications[1] and the PPWG proposed that the latter term should be used in the Expert Committee report.

Actual abuse and/or abuse liability (likelihood of abuse)

This section includes reports of actual abuse. Such information was found in Section 8 (Epidemiology of drug use and abuse) and could be inferred from Section 12 (Illicit manufacture, illicit traffic, and related information) of the critical review. Information on the existence of national control measures (part of section 9 of the critical review) was also included in this section because it was assumed that actual or probable abuse in an individual country would result in the introduction of national control measures. If there was actual abuse, its nature and the magnitude of the associated public health and social problems were noted.

If there was insufficient evidence of actual abuse of the substance under review, this section was used to record the Expert Committee's judgement on the abuse liability (likelihood of abuse) on the basis of information concerning limited abuse, pharmacological profile, dependence potential, and other pertinent facts (see, for example, the section above on "Similarity"). This overall judgement was summarized in the "Recommendation" section. It should be noted that the term "abuse liability" is used in this section of the proposed format to mean likelihood of abuse, whereas in the critical review it was used to mean dependence potential.

Therapeutic usefulness

In arriving at the overall assessment of therapeutic usefulness, the Expert Committee considered a number of factors, including extent of use, evidence for effectiveness, unwanted effects, cost, severity and prevalence of the disorders to be treated, availability of alternative treatments, and the nature of the health care system and culture in which the treatment is to be used. In order to avoid repetition in the review of individual compounds, the Committee decided to discuss the therapeutic usefulness of the barbiturate compounds as a class. This discussion is presented in section 2 below. In the review of individual barbiturate compounds, only the extent of use is indicated

[1] For example: WHO Technical Report Series No. 577, 1975; Nomenclature and classification of drug and alcohol-related problems: a WHO Memorandum. *Bulletin of the World Health Organization*, **59:** 225–242 (1981).

along with a statement on whether the compound is rated low, moderate, or high in terms of its therapeutic usefulness.

Recommendation

For each drug under review, the Committee made a recommendation for or against scheduling in accordance with Article 2, paragraph 4 of the Convention on Psychotropic Substances, and this recommendation is presented in this final section.

2. METHODS USED IN ASSESSING THE THIRTY-ONE BARBITURATES

In reviewing the individual substances, certain general principles were adopted. For instance, there was no discussion of isomers of the drugs, although a statement was made indicating whether the substances existed as racemic mixtures. This was done because the separation of the isomers of the barbiturates is difficult and the production of large quantities of one type of isomer would be very costly and impractical. Moreover, none of the marketed barbiturates under discussion is sold as a pure isomer.

Another problem that arose concerned the fact that only few specific pharmacological data were available for many of the substances under review. Thus, the clinical pharmacological classification of each substance (sedative–hypnotic, anticonvulsant, intravenous anaesthetic) was used to make logical assumptions concerning its effects on the central nervous system or its pharmacokinetic profile.

Finally, in evaluating the therapeutic usefulness of the main barbiturate substances under review, the Committee considered that they could be assessed in three major groups:

(*a*) *The ultra-short-acting barbiturates.* These are used principally as intravenous anaesthetics or to induce anaesthesia. Their use is mainly in hospitals. They are effective, relatively easy to use, and safe in skilled hands, and are very widely used in surgery. There are no comparable alternatives. Overall, their therapeutic usefulness for this purpose was considered by the Committee to be high.

(*b*) *The intermediate-acting barbiturates.* These are used principally as hypnotics and daytime sedatives. Some are included in combination products with analgesics or with a wide variety of

other drugs. Combination preparations containing intermediate-acting barbiturates are widely regarded as undesirable, although as hypnotics and sedatives, the barbiturates are effective. They were widely used in the past but their use is declining now because of dangers such as abuse, lower margin of safety leading to fatality, and drug interactions resulting from the stimulation of microsomal enzymes. Moreover, effective and safer alternatives have become available. Because of these factors the Committee considered their therapeutic usefulness to be lower than that of other available alternatives.

(*c*) *Other barbiturates.* These are mostly substances with a duration of action longer than that of intermediate-acting barbiturates, and they are used in the management of epilepsy. They have more pronounced anticonvulsant effects at doses that do not produce major sedation. They are effective and widely used, particularly in developing countries where epilepsy is more common. Their ease of use renders them suitable for administration by less skilled health workers. There has been some tendency in developed countries to replace them with alternatives that are less sedating and are less likely to result in abuse; however, the alternatives are more costly and complicated to use. Overall, because of their value in a major public health problem, the Committee assessed their therapeutic usefulness as high.

3. ASSESSMENT OF INDIVIDUAL SUBSTANCES

3.1 Allobarbital

3.1.1 *Substance identification*

Allobarbital (INN, CAS-52-43-7), chemically 5,5-diallybarbituric acid, is also known as allobarbitone, diallylbarbitone, diallylbarbituric acid, diallylmalonylurea, and diallymalum.

3.1.2 *Similarity to already scheduled substances*

Allobarbital has been classified pharmacologically as an intermediate-acting sedative–hypnotic barbiturate with a profile similar to that of pentobarbital. As it is a hypnotic, it is presumed that dose-related drowsiness, vertigo, confusion, and incoordination

can occur. The drug, like other barbiturates, is metabolized by hepatic microsomal enzymes and stimulates the production of these enzymes.

3.1.3 *Effects on the central nervous system and mental functions*

The drug produces typical barbiturate-like sedative and hypnotic effects on the central nervous system. As it is a hypnotic, it is presumed that tolerance, both natural and functional, can occur. Cross-tolerance may occur to other barbiturates, ethanol, and other sedative–hypnotic drugs.

3.1.4 *Dependence potential*

With the exception of one clinical report on a single patient, there is no information on the ability of allobarbital to induce physical or psychic dependence, in either animals or man in controlled laboratory studies.

3.1.5 *Actual abuse and/or abuse liability (likelihood of abuse)*

A number of cases involving the abuse of allobarbital have been reported from Belgium and the Federal Republic of Germany, while Austria and Czechoslovakia have reported sporadic cases of abuse. These reports have mainly concerned combination preparations. No government has reported on any public health or social problems caused by this substance.

There have been reports of seizures of small amounts of the drug from the Republic of Korea and the United States of America. The Federal Republic of Germany, too, has reported a notable number of cases of forged prescriptions and thefts involving allobarbital.

3.1.6 *Therapeutic usefulness*

Allobarbital is used as a sedative and hypnotic. It is also combined in analgesic preparations, although the enhanced efficacy of such mixtures has not been firmly established. The drug or combinations containing it have been reported to be registered and/or available on the market in 26 countries. Over the past few years only modest amounts of the drug have been used. The Committee

considered the therapeutic usefulness of this drug to be relatively low.

3.1.7 *Recommendation*

The Committee found that there was sufficient evidence (sections 3.1.2–3.1.5) that allobarbital is being, or is likely to be, abused so as to constitute a public health and social problem warranting the placing of the substance under international control in the Convention on Psychotropic Substances.

On the basis of its pharmacological profile, dependence potential, and on limited evidence of actual abuse, the Committee rated the likelihood of abuse of allobarbital as moderate. The degree of seriousness of the public health and social problems associated with its abuse was also found to be moderate and its therapeutic usefulness relatively low.

In the light of this assessment, the Committee recommended that allobarbital be placed in Schedule IV.

3.2 Aprobarbital

3.2.1 *Substance identification*

Aprobarbital (INN, CAS-77-02-1), chemically 5-allyl-5-isopropylbarbituric acid or allylisopropylmalonylurea, is also known as allypropymal, allypropymalum, aprobarbitalum, and aprobarbitone. The substance is a racemic mixture.

3.2.2 *Similarity to already scheduled substances*

Aprobarbital has been classified pharmacologically as an intermediate-acting sedative–hypnotic barbiturate with a profile similar to that of pentobarbital. As it is a hypnotic, it is presumed that dose-related drowsiness, vertigo, confusion, and incoordination can occur. The drug, like other barbiturates, is metabolized by hepatic microsomal enzymes and stimulates the production of these enzymes.

3.2.3 *Effects on the central nervous system and mental functions*

The drug produces typical barbiturate-like sedative–hypnotic effects on the central nervous system. As it is a hypnotic, it is

presumed that tolerance, both natural and functional, can occur. Cross-tolerance may occur to other barbiturates, ethanol, and other sedative–hypnotic drugs.

3.2.4 *Dependence potential*

There is no specific information available on the ability of aprobarbital to induce physical or psychic dependence, in either animals or man in controlled laboratory studies.

3.2.5 *Actual abuse and/or abuse liability (likelihood of abuse)*

There have been sporadic reports on the abuse of aprobarbital from Finland, Federal Republic of Germany, Norway, and the United States of America. These reports have mainly concerned combination preparations and no government has reported any public health or social problems caused by this substance. Seven countries reported that the drug is under national control.

There have been reports of seizures of small amounts of the drug from Norway and the United States of America. The Federal Republic of Germany reported a few punishable offences involving aprobarbital from 1982 to 1984.

3.2.6 *Therapeutic usefulness*

Aprobarbital is used as a sedative and hypnotic and has the same efficacy as other barbiturates in this regard. The drug or combination products containing it have been reported to be registered and/or available on the market in thirteen countries. Over the past two years modest amounts of the drug have been consumed.

3.2.7 *Recommendation*

The Committee found that there was insufficient evidence that aprobarbital is being, or is likely to be, abused so as to constitute a public health and social problem warranting the placing of the substance under international control.

On the basis of the limited data concerning its pharmacological profile, dependence potential, and actual abuse, the Committee rated the likelihood of abuse of aprobarbital as moderate. The degree of the public health and social problems associated with the drug was

found to be low. The Committee rated the therapeutic usefulness of aprobarbital to be relatively low.

In the light of this assessment, the Committee recommended against scheduling of the drug.

3.3 Benzobarbital

3.3.1 *Substance identification*

Benzobarbital (INN, CAS-744-80-9), chemically 1-benzoyl-5-ethyl-5-phenylbarbituric acid, is also known as benzobarbitone, benzonal, and benzonalum. It is a racemic mixture.

3.3.2 *Similarity to already scheduled substances*

Benzobarbital has been classified pharmacologically as an anticonvulsant barbiturate with a profile similar to that of phenobarbital. Data on benzobarbital are insufficient to determine whether the drug produces drowsiness, vertigo, confusion, and incoordination. The drug, like other barbiturates, is metabolized by hepatic microsomal enzymes and stimulates the production of these enzymes.

3.3.3 *Effects on the central nervous system and mental functions*

The available data are insufficient to determine whether benzobarbital produces typical barbiturate-like depression of the central nervous system.

3.3.4 *Dependence potential*

There is no information available on the ability of benzobarbital to induce physical or psychic dependence, in either animals or man.

3.3.5 *Actual abuse and/or abuse liability (likelihood of abuse)*

There are no reports of abuse of benzobarbital. It is, however, under national control in five countries. There is no evidence of illicit trafficking or manufacture.

3.3.6 *Therapeutic usefulness*

There are reports that the drug is effective in the treatment of epilepsy. However, it appears that the drug is not marketed. The

Committee found the therapeutic usefulness of benzobarbital to be high for the indicated use.

3.3.7 *Recommendation*

The Committee found that there was insufficient evidence that benzobarbital is being, or is likely to be, abused so as to constitute a public health and social problem warranting the placing of the substance under international control.

On the basis of the limited data concerning its pharmacological profile, dependence potential, and actual abuse, the Committee rated the likelihood of abuse of benzobarbital as low. The degree of the public health and social problems associated with the drug was found to be low. The therapeutic usefulness for the indicated use was found to be high.

In the light of this assessment, the Committee recommended against scheduling of the drug.

3.4 Butalbital[1]

3.4.1 *Substance identification*

Butalbital (INN, CAS-77-26-9), chemically 5-allyl-5-isobutylbarbituric acid, is also known as alisobumal, alisobumalum, allylbarbital, allylbarbituric acid, itobarbital, and tetrallobarbital. It is a racemic mixture.

3.4.2 *Similarity to already scheduled substances*

Butalbital has been classified pharmacologically as an intermediate-acting sedative–hypnotic barbiturate with a profile similar to that of pentobarbital. As it is a hypnotic, it is presumed that dose-related drowsiness, vertigo, confusion, and incoordination can occur. The drug, like other barbiturates, is metabolized by hepatic microsomal enzymes and stimulates the production of these enzymes.

[1] It should be noted that the name butalbital has also been applied to talbutal, the 5-butyl analogue of butalbital (see section 3.25).

3.4.3 *Effects on the central nervous system and mental functions*

Butalbital produces a typical barbiturate-like depression of the central nervous system. As it is a hypnotic, it is presumed that tolerance, both natural and functional, may occur. Cross-tolerance may occur to other barbiturates, ethanol, and other sedative–hypnotic agents.

3.4.4 *Dependence potential*

With the exception of a single case report, there is no specific information available on the ability of butalbital to induce physical or psychic dependence, in either animals or man in controlled laboratory studies.

One case has been reported of severe withdrawal symptoms in an infant after intrauterine exposure to butalbital. The withdrawal manifestations, including seizures, were relieved by phenobarbital.

3.4.5 *Actual abuse and/or abuse liability (likelihood of abuse)*

There have been reports in the literature of actual abuse of butalbital and urine samples positive for butalbital use have been found among probationary prisoners and methadone maintenance patients.

Seven countries have reported some abuse of butalbital, with most cases involving combination products. One government reported that this abuse caused some public health and social problems. Eight countries reported that the drug is under national control. There have been reports of illicit trafficking from seven countries.

3.4.6 *Therapeutic usefulness*

Butalbital has been used as both a sedative and as a hypnotic. It is one component of a number of preparations containing non-steroidal anti-inflammatory agents (e.g., one combination preparation contains butalbital, acetylsalicylic acid, phenacetin, and caffeine), which are widely used for the treatment of headache. There is no convincing evidence that barbiturates contribute significantly to the analgesic activity of these preparations. The drug and/or its preparations are reported to be marketed or are available in 27 countries. Over the past two years, significant amounts of butalbital

have been sold in several countries. The Committee rated the therapeutic usefulness of butalbital as relatively low.

3.4.7 *Recommendation*

The Committee found sufficient evidence that butalbital has been, and is likely to be, abused so as to constitute a public health and social problem warranting the placing of the substance under international control in the Convention on Psychotropic Substances.

On the basis of its pharmacological profile, dependence potential, and evidence of actual abuse, the Committee rated the likelihood of abuse of butalbital as moderate. The degree of the seriousness of the public health and social problems associated with its abuse was found to be high and its therapeutic usefulness relatively low.

In the light of this assessment, the Committee recommended that butalbital be placed in Schedule III.

3.5 Butallylonal

3.5.1 *Substance identification*

Butallylonal (CAS-1142-70-7), chemically 5-(2-bromoallyl)-5-sec-butyl-barbituric acid, is also known as sonbutal. It is a racemic mixture.

3.5.2 *Similarity to already scheduled substances*

Butallylonal has been classified pharmacologically as an intermediate-acting sedative–hypnotic barbiturate with a profile similar to pentobarbital. As it is a hypnotic, it is presumed that dose-related drowsiness, vertigo, confusion, and incoordination can occur. The drug, like other barbiturates, is probably metabolized by hepatic microsomal enzymes and may stimulate the production of these enzymes.

3.5.3 *Effects on the central nervous system and mental functions*

Since the drug has been used as a hypnotic it may be presumed to depress the central nervous system in the same way as other barbiturates. As there are no data of its effects, no further assessment can be made.

3.5.4 *Dependence potential*

There is no information available on the ability of butallylonal to induce physical or psychic dependence, in either animals or man in controlled laboratory studies.

3.5.5 *Actual abuse and/or abuse liability (likelihood of abuse)*

No actual cases of abuse have been reported and there is no indication of illicit trafficking of the drug. Four countries reported the drug to be under national control.

3.5.6 *Therapeutic usefulness*

The drug has been used therapeutically as a central nervous system depressant and as a hypnotic. Two countries reported that the drug is available on the market and one that it is registered. There is no indication that the drug has anything but minor use. The Committee rated the therapeutic usefulness of butallylonal as relatively low.

3.5.7 *Recommendation*

The Committee found that there was insufficient evidence that butallylonal is being, or is likely to be, abused so as to constitute a public health and social problem warranting the placing of the substance under international control.

On the basis of the limited data concerning its pharmacological profile, dependence potential, and actual abuse, the Committee rated the likelihood of abuse of butallylonal as indeterminate. The degree of the public health and social problems associated with the drug was also found to be low as was its therapeutic usefulness.

In the light of this assessment, the Committee recommended against scheduling of the drug.

3.6 Buthalital sodium

3.6.1 *Substance identification*

Buthalital sodium (INN, CAS-510-90-7), chemically 5-allyl-5-isobutyl-2-thiobarbituric acid sodium salt, is also known as butalital sodico, thialbutone sodium, thiobutone sodium, and buthalitone sodium.

3.6.2 *Similarity to already scheduled substances*

Buthalital sodium is classified as an ultra-short-acting barbiturate and was formerly used as an intravenous anaesthetic. No barbiturate of this type is currently scheduled. Dose-related drowsiness, vertigo, confusion, and incoordination can occur. The drug, like other barbiturates, is metabolized by hepatic microsomal enzymes and stimulates production of these enzymes.

3.6.3 *Effects on the central nervous system and mental functions*

Buthalital sodium is a potent depressant of the central nervous system. It rapidly produces anaesthesia of a short duration. Tolerance, both natural and functional, can occur. Cross-tolerance may occur to other barbiturates, ethanol, and other sedative–hypnotic drugs.

3.6.4 *Dependence potential*

There is no specific information available on the ability of buthalital to induce physical or psychic dependence in either animals or man in controlled laboratory studies.

3.6.5 *Actual abuse and/or abuse liability (likelihood of abuse)*

No cases of actual abuse, seizures, or production of the drug in clandestine laboratories have been reported. In five countries it is under national legislative control.

3.6.6 *Therapeutic usefulness*

Buthalital has been used as an anaesthetic agent. There is no indication that the drug is currently marketed. For its indicated use, the Committee rated the therapeutic usefulness of buthalital as high.

3.6.7 *Recommendation*

The Committee found that there was insufficient evidence that buthalital is being, or is likely to be, abused so as to constitute a public health and social problem warranting the placing of the substance under international control.

On the basis of the limited data concerning its pharmacological profile, dependence potential, and actual abuse, the Committee rated

the likelihood of abuse of buthalital as low. The degree of the public health and social problems associated with the drug was found to be low and its therapeutic usefulness high.

In the light of this assessment, the Committee recommended against scheduling of the drug.

3.7 Butobarbital

3.7.1 *Substance identification*

Butobarbital (CAS-77-28-1), chemically 5-butyl-5-ethylbarbituric acid, is also known as butethal, butobarb, butobarbitalum, and butobarbitone. It is a racemic mixture.

3.7.2 *Similarity to already scheduled substances*

Butobarbital has been pharmacologically classified as an intermediate-acting sedative–hypnotic barbiturate with a profile similar to pentobarbital. As it is a hypnotic, it is presumed that dose-related drowsiness, vertigo, confusion, and incoordination can occur. The drug, like other barbiturates, is metabolized by hepatic microsomal enzymes and stimulates the production of these enzymes.

3.7.3 *Effects on the central nervous system and mental functions*

Butobarbital produces typical barbiturate-like sedative–hypnotic effects on the central nervous system. As it is a hypnotic, it is presumed that tolerance, both natural and functional, may occur. Cross-tolerance may occur to other barbiturates, ethanol, and other sedative–hypnotic drugs.

3.7.4 *Dependence potential*

There is no specific information available on the ability of butobarbital to induce physical or psychic dependence, either in animals or man in controlled laboratory studies.

3.7.5 *Actual abuse and/or abuse liability (likelihood of abuse)*

Belgium reported notable cases of abuse of preparations containing butobarbital. The drug was also reported to be abused

in Nigeria. Minor cases of abuse were reported from Argentina, Czechoslovakia, and Hungary. New Zealand also reported a few suicides and one accidental death in the years 1982–85 associated with the abuse of the substance. No government reported any public health or social problems caused by this substance. Butobarbital is under national legislative control in twelve countries. There have been reports of illicit trafficking from three countries.

3.7.6 *Therapeutic usefulness*

Butobarbital was introduced as a hypnotic in 1931, and it continues to be used as a sedative–hypnotic in many countries. It is registered and/or is available on the market in 37 countries. Over the past two years, significant amounts of butobarbital have been sold in several countries. The Committee rated the therapeutic usefulness of butobarbital as relatively low.

3.7.7 *Recommendation*

The Committee found that there was sufficient evidence that butobarbital is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control in the Convention on Psychotropic Substances.

On the basis of its pharmacological profile, dependence potential, and evidence of actual abuse, the Committee rated the likelihood of abuse of butobarbital as moderate. The degree of seriousness of the public health and social problems associated with its abuse was also found to be moderate and its therapeutic usefulness relatively low.

In the light of this assessment, the Committee recommended that butobarbital be placed in Schedule IV.

3.8 Cyclopentobarbital

3.8.1 *Substance identification*

Cyclopentobarbital (CAS-76-68-6), chemically 5-allyl-5-(2-cyclopenten-1-yl)barbituric acid, is also known as cyclopentobarbitone and cyclopentenylallyl barbituric acid.

3.8.2 *Similarity to already scheduled substances*

Cyclopentobarbital has been pharmacologically classified as an intermediate-acting sedative–hypnotic barbiturate with a profile

similar to that of pentobarbital. As it is a hypnotic, it is presumed that dose-related drowsiness, vertigo, confusion, and incoordination can occur. The drug, like other barbiturates, may be metabolized by hepatic microsomal enzymes and may stimulate the production of these enzymes.

3.8.3 *Effects on the central nervous system and mental functions*

Few data are available concerning the pharmacology of cyclopentobarbital. Since it has been used as a hypnotic, it may be assumed to produce typical barbiturate-like sedative–hypnotic effects on the central nervous system. As it is a hypnotic, it is presumed that tolerance, both natural and functional, may occur. Cross-tolerance may occur to other barbiturates, ethanol, and other sedative–hypnotic drugs.

3.8.4 *Dependence potential*

There is no specific information available on the ability of cyclopentobarbital to induce physical or psychic dependence, in either animals or man in controlled laboratory studies.

3.8.5 *Actual abuse and/or abuse liability (likelihood of abuse)*

The Warsaw Poison Control Centre reported some cases of overdose in 1983 and 1985. The Federal Republic of Germany reported one case of abuse and a few criminal offences related to cyclopentobarbital. There have been no seizures or reports of production of the drug in clandestine laboratories.

3.8.6 *Therapeutic usefulness*

Cyclopentobarbital is used as a sedative and a hypnotic and has the same efficacy as other barbiturates in this regard. The drug or combination products containing it have been reported to be registered and/or available on the market in two countries. Over the last two years only small amounts of the drug have been used. The Committee rated the therapeutic usefulness of cyclopentobarbital as relatively low.

3.8.7 *Recommendation*

The Committee found that there was insufficient evidence that cyclopentobarbital is being, or is likely to be, abused so as to constitute a public health and social problem warranting the placing of the substance under international control.

On the basis of the limited data concerning its pharmacological profile, dependence potential, and actual abuse, the Committee rated the likelihood of abuse of cyclopentobarbital as indeterminate. The degree of the public health and social problems associated with the drug was also found to be low as was its therapeutic usefulness.

In the light of this assessment, the Committee recommended against scheduling of the drug.

3.9 Difebarbamate

3.9.1 *Substance identification*

Difebarbamate (INN, CAS-15687-09-9), chemically 1,3-bis (3-butoxy-2-2 hydroxy-propyl)-5 phenylbarbituric acid dicarbamate, has no common names. The substance is a racemic mixture.

3.9.2 *Similarity to already scheduled substances*

Difebarbamate is a derivative of phenobarbital in which both nitrogens are substituted with bulky butoxycarbamyolpropyl groups, which are allegedly hard to split. Because of these substitutions the compound loses its barbiturate-like pharmacological profile. It is not similar to other barbiturates that are already scheduled.

3.9.3 *Effects on the central nervous system and mental functions*

The pharmacology of difebarbamate cannot be evaluated. No consistent data are available. In fifteen different tests, the substance was found to be completely inactive; in thirteen of those fifteen tests the drug was found to have no effects on the central nervous system. It must be remembered, however, that in these tests difebarbamate was administered only orally and the amount of the substance absorbed from the gastrointestinal tract was unknown.

3.9.4 *Dependence potential*

There is no information available on the ability of difebarbamate to induce physical or psychic dependence, in either animals or man in controlled laboratory studies.

3.9.5 *Actual abuse and/or abuse liability (likelihood of abuse)*

Isolated cases of abuse have been reported from France, but it is not clear whether these refer to difebarbamate or to tetrabamate, which is a complex containing one molecule of difebarbamate. There was one report of illicit trafficking, and the drug was reported to be under national control in five countries.

3.9.6 *Therapeutic usefulness*

There is no claim for the therapeutic use of the substance as a single preparation. It is a constituent of tetrabamate, a complex containing 50% febarbamate, 35.7% difebarbamate, and 14.3% phenobarbital. Information on tetrabamate is insufficient to judge its usefulness. However, tetrabamate is available in several countries and large amounts of the drug are sold, especially in France. The Committee rated the therapeutic usefulness of difebarbamate as low.

3.9.7 *Recommendation*

The Committee found that there was insufficient evidence at this time that difebarbamate is being, or is likely to be, abused so as to constitute a public health and social problem warranting the placing of the substance under international control.

On the basis of the limited data concerning its pharmacological profile, dependence potential, and actual abuse, the Committee rated the likelihood of abuse of difebarbamate as low. The degree of the public health and social problems associated with the drug was found to be low as was its therapeutic usefulness.

In the light of this assessment, the Committee recommended against scheduling of the drug.

3.10 Febarbamate

3.10.1 *Substance identification*

Febarbamate (INN, CAS-13246-02-1), chemically 1-(3′-butoxy-2′-hydroxypropyl)-5-ethyl-5-phenylbarbituric acid carbamate, is also known as phebarbamate, and phenobamate. It is a racemic mixture.

3.10.2 *Similarity to already scheduled substances*

Febarbamate is a derivative of phenobarbital in which one nitrogen is substituted with a butoxylcarbamoylpropyl group. It has been reported that the drug is extensively metabolized in the body, but not to phenobarbital. The manufacturer claims that because of this bulky substitution, phenobarbital loses its typical pharmacological profile and febarbamate is completely devoid of sedative–hypnotic effects. Most of the reported pharmacological data concern tetrabamate, which is a stable complex containing two molecules of febarbamate. The drug is not similar to any of the already scheduled substances.

3.10.3 *Effects on the central nervous system and mental functions*

Pharmacological data from animal studies concerning febarbamate have been provided by the manufacturer. The drug is reported to be devoid of sedative–hypnotic and toxic effects after oral administration. However, an intraperitoneal LD_{50} of 277 mg/kg of body weight was reported for mice. Unfortunately, no report of observed signs and symptoms was given. It is possible that the drug is poorly absorbed in the gastrointestinal tract and/or rapidly metabolized.

3.10.4 *Dependence potential*

There is no information available on the ability of febarbamate to induce physical or psychic dependence, in either animals or man in controlled laboratory studies.

3.10.5 *Actual abuse and/or abuse liability (likelihood of abuse)*

Isolated cases of abuse in France have been reported but it is not clear whether these involved the substance itself or the complex

tetrabamate. In the Congo, the drug was reported to be found in illicit trafficking. It is under national control in five countries.

3.10.6 *Therapeutic usefulness*

Febarbamate has been reported to be a thymoanaleptic and to be of use in the treatment of agitation in the elderly. The Committee felt that there was insufficient information to judge the usefulness of febarbamate. Large quantities of the drug are used either as a pure drug or as a constituent of the complex tetrabamate, particularly in France.

3.10.7 *Recommendation*

The Committee found that there was insufficient evidence that febarbamate is being, or is likely to be, abused so as to constitute a public health and social problem warranting the placing of the substance under international control.

On the basis of the very limited data concerning its pharmacological profile, dependence potential, and actual abuse, the Committee rated the likelihood of abuse of febarbamate as indeterminate. The degree of the public health and social problems associated with the drug was found to be low and its therapeutic usefulness remains to be established.

In the light of this assessment, the Committee recommended against scheduling of the drug. However, owing to the large consumption of the drug, it was felt that continued surveillance was warranted.

3.11 Heptabarb

3.11.1 *Substance identification*

Heptabarb (INN, CAS-509-86-4), chemically 5-(1-cyclohepten-1-yl)-5-ethylbarbituric acid, is also known as heptabarbe, heptabarbital, heptabarbitone, and heptamalum. It is a racemic mixture.

3.11.2 *Similarity to already scheduled substances*

Heptabarb has been classified pharmacologically as an intermediate-acting sedative–hypnotic barbiturate with a profile

similar to that of pentobarbital. As it is a hypnotic, it is presumed that dose-related drowsiness, vertigo, confusion and incoordination can occur. The drug, like other barbiturates, is metabolized by hepatic microsomal enzymes and stimulates the production of these enzymes.

3.11.3 *Effects on the central nervous system and mental functions*

The drug produces typical barbiturate-like sedative–hypnotic effects on the central nervous system. As it is a hypnotic, it is presumed that tolerance, both natural and functional, can occur. Cross-tolerance may occur to other barbiturates, ethanol, and other sedative–hypnotic drugs.

3.11.4 *Dependence potential*

There is no information on the ability of heptabarb to induce physical or psychic dependence in either animals or man in controlled laboratory studies.

3.11.5 *Actual abuse and/or abuse liability (likelihood of abuse)*

There have been isolated cases of abuse of heptabarb in Belgium, Federal Republic of Germany, Norway, and the United States of America. The drug is under national control in eight countries. There have been no reports of illicit manufacture, illicit trafficking, or seizures of the drug, but there have been some cases of prescription forgery in recent years. No government has reported any social or public health problems caused by this substance.

3.11.6 *Therapeutic usefulness*

Heptabarb is used as a hypnotic and a sedative. It is produced or marketed in nine countries. The Committee rated the therapeutic usefulness of this drug as relatively low.

3.11.7 *Recommendation*

The Committee found that there was insufficient evidence that heptabarb is being, or is likely to be, abused so as to constitute a public health and social problem warranting the placing of the substance under international control.

On the basis of the limited data concerning its pharmacological profile, dependence potential, and actual abuse, the Committee rated the likelihood of abuse of heptabarb as moderate. The degree of the public health and social problems associated with the drug was found to be low as was its therapeutic usefulness.

In the light of this assessment, the Committee recommended against scheduling of the drug.

3.12 Hexethal

3.12.1 *Substance identification*

Hexethal (CAS 77-30-5), chemically 5-ethyl-5-hexylbarbiturate, has no common names. It is a racemic mixture.

3.12.2 *Similarity to already scheduled substances*

Few data are available on hexethal. It has been classified pharmacologically as a short-acting sedative–hypnotic barbiturate. As it is a hypnotic agent, it is presumed that dose-related drowsiness, vertigo, confusion, and incoordination can occur. No data are available on its metabolism or pharmacokinetics.

3.12.3 *Effects on the central nervous system and mental functions*

Since the drug was originally marketed as a sedative and a hypnotic, it may be assumed to produce typical barbiturate-like sedative–hypnotic effects on the central nervous system. As it is a hypnotic, it is presumed that tolerance, both natural and functional, may occur. Cross-tolerance may occur to other barbiturates, non-barbiturate hypnotics, ethanol, and other sedative–hypnotic drugs.

3.12.4 *Dependence potential*

There is no information on the ability of hexethal to induce physical or psychic dependence in either animals or man in controlled laboratory studies.

3.12.5 *Actual abuse and/or abuse liability (likelihood of abuse)*

There have been no reports on the abuse of hexethal. The drug is under national control in five countries. There have been no

reports of illicit manufacture, illicit trafficking, or seizures of the drug.

3.12.6 *Therapeutic usefulness*

Hexethal has been used as a sedative–hypnotic but no information on its therapeutic use has been found. According to the information available to the Committee, this substance is no longer marketed. It is registered in five countries, but is not available on the market. The Committee rated the therapeutic usefulness of hexethal as relatively low.

3.12.7 *Recommendation*

The Committee found that there was insufficient evidence that hexethal is being, or is likely to be, abused so as to constitute a public health and social problem warranting the placing of the substance under international control.

On the basis of the very limited data concerning its pharmacological profile, dependence potential, and actual abuse, the Committee rated the likelihood of abuse of hexethal as indeterminate. The degree of the public health and social problems associated with the drug was found to be low, as was its therapeutic usefulness.

In the light of this assessment, the Committee recommended against scheduling of the drug.

3.13 Hexobarbital

3.13.1 *Substance identification*

Hexobarbital (INN, CAS 56-29-1), chemically 5-(1-cyclohexen-1-yl)-1,5-dimethylbarbituric acid, is also known as ciclobarbital, enhexymal, enhexymalum, enimal, esobarbital, hexabarbital, hexobarbitalum, hexobarbitone, methexenyl, methyl-cyclo-hexenylmethyl-barbitusaure, methylhexabarbital, methylhexabital. The substance is a racemic mixture.

3.13.2 *Similarity to already scheduled substances*

Hexobarbital has been classified as a short-acting intravenous anaesthetic agent. As such it is not similar to any of the already

scheduled barbiturates. The drug has also been used orally as a sedative and a hypnotic. It produces dose-related drowsiness, vertigo, confusion, and incoordination. It is metabolized by hepatic microsomal enzymes and stimulates the production of these enzymes. Thus, hexobarbital is similar to other barbiturates in this regard.

3.13.3 *Effects on the central nervous system and mental functions*

The drug produces typical barbiturate-like effects on the central nervous system. Tolerance, both natural and functional, does occur. Cross-tolerance occurs to other barbiturates, ethanol, and to other sedative–hypnotic drugs.

3.13.4 *Dependence potential*

It has been demonstrated in animal experiments that rats seek intravenous self administration of hexobarbital, indicating that it has dependence potential.

3.13.5 *Actual abuse and/or abuse liability (likelihood of abuse)*

Isolated cases of abuse have been reported by four countries. The drug is under national control in four countries. Several reports of illicit trafficking and/or seizures have been reported from six countries. There were no reports of clandestine manufacture.

3.13.6 *Therapeutic usefulness*

Hexobarbital is used orally as a hypnotic and a sedative. It was formerly used as an induction anaesthetic with similar effects and toxicity to those of thiopental sodium. It is also widely used as a laboratory agent for measuring the potentiation of sleeping time.

Hexobarbital is produced and/or marketed in seven countries. In most countries where it is marketed, hexobarbital is available on prescription only, with no refill.

The Committee rated its therapeutic usefulness as a sedative–hypnotic as relatively low. Its usefulness as an intravenous anaesthetic agent and as a laboratory agent for measuring the potentiation of sleeping time, was rated as relatively high.

3.13.7 *Recommendation*

The Committee found that there was insufficient evidence that hexobarbital is being, or is likely to be, abused so as to constitute a public health and social problem warranting the placing of the substance under international control.

On the basis of the data concerning its pharmacological profile, dependence potential, and actual abuse, the Committee rated the likelihood of abuse of hexobarbital as moderate. The degree of the public health and social problems associated with the drug was found to be low as was its therapeutic usefulness as a sedative–hypnotic. As an intravenous anaesthetic agent and laboratory standard its usefulness was rated as relatively high.

In the light of this assessment, the Committee recommended against scheduling of the drug.

3.14 Mephebarbital

3.14.1 *Substance identification*

Mephebarbital (CAS 76-94-8), chemically 5-methyl-5-phenylbarbituric acid, is also known as heptobarbital, heptobarbitone, heptobarbitalum, and phenylmethylbarbituric acid. The substance is a racemic mixture.

3.14.2 *Similarity to already scheduled substances*

Mephebarbital has been classified pharmacologically as an anticonvulsant barbiturate with a profile similar to that of phenobarbital. As it is an anticonvulsant barbiturate, it is presumed that dose-related drowsiness, vertigo, confusion, and incoordination can occur. The drug, like other barbiturates, is metabolized by hepatic microsomal enzymes and stimulates the production of these enzymes.

3.14.3 *Effects on the central nervous system and mental functions*

The drug produces typical barbiturate-like anticonvulsant and depressant effects on the central nervous system. As it is an anticonvulsant barbiturate, it is presumed that tolerance, both natural and functional, can occur. Cross-tolerance may occur to other barbiturates, ethanol, and other sedative–hypnotic drugs.

3.14.4 *Dependence potential*

There is no information on the ability of mephebarbital to induce physical or psychic dependence in either animals or man in controlled laboratory studies.

3.14.5 *Actual abuse and/or abuse liability (likelihood of abuse)*

One country reported an isolated case of actual abuse of mephebarbital. The drug is under national control in five countries. There have been no reports of illicit manufacture, illicit trafficking, or seizures of this drug.

3.14.6 *Therapeutic usefulness*

Mephebarbital has been used as an anticonvulsant, but it may not be as effective as phenobarbital for this purpose. It is also used as a sedative. The substance is currently manufactured and marketed only in France. The Committee rated the therapeutic usefulness of mephebarbital as an anticonvulsant as moderate.

3.14.7 *Recommendation*

The Committee found that there was insufficient evidence that mephebarbital is being, or is likely to be, abused so as to constitute a public health and social problem warranting the placing of the substance under international control.

On the basis of the limited data concerning its pharmacological profile, dependence potential, and actual abuse, the Committee rated the likelihood of abuse of mephebarbital as moderate. The degree of the public health and social problems associated with the drug was found to be low and its therapeutic usefulness intermediate.

In the light of this assessment, the Committee recommended against scheduling of the drug.

3.15 Metharbital

3.15.1 *Substance identification*

Metharbital (INN, CAS-50-11-3), chemically 5,5-diethyl-1-methylbarbituric acid, is also known as endiemal and metharbitone. The substance is a racemic mixture.

3.15.2 *Similarity to already scheduled substances*

Metharbital has been classified pharmacologically as an anticonvulsant barbiturate with a profile similar to that of phenobarbital. As it is an anticonvulsant barbiturate, it is presumed that dose-related drowsiness, vertigo, confusion and incoordination can occur. The drug, like other barbiturates, is metabolized by hepatic microsomal enzymes and stimulates the production of these enzymes. Metharbital is metabolized to barbital which is controlled in Schedule IV of the Convention on Psychotropic Substances.

3.15.3 *Effects on the central nervous system and mental functions*

The drug produces typical barbiturate-like anticonvulsant sedative–hypnotic effects on the central nervous system. As it is a hypnotic, it is presumed that tolerance, both natural and functional, can occur. Cross-tolerance may occur to other barbiturates, ethanol, and other sedative–hypnotic drugs.

3.15.4 *Dependence potential*

Metharbital produces physical dependence of the barbiturate type, but there is no evidence on the ability of metharbital to induce psychic dependence in either animals or man in controlled laboratory studies.

3.15.5 *Actual abuse and/or abuse liability (likelihood of abuse)*

There have been isolated reports on the abuse of metharbital from Norway and the United States of America. It is under national control in six countries. There have been sporadic reports of illicit trafficking and seizures of metharbital in the United States of America but not of clandestine manufacture. There were no reports of any public health and social problems caused by this substance.

3.15.6 *Therapeutic usefulness*

Metharbital is used as an anticonvulsant for the control of epilepsy. It has also been reported to be effective for infantile myoclonic spasm. The drug is marketed only in New Zealand and the United States of America, and only small amounts of the drug are used. The Committee rated the therapeutic usefulness for the treatment of epilepsy and infantile myoclonic spasm as high.

3.15.7 *Recommendation*

The Committee found that there was insufficient evidence that metharbital is being, or is likely to be, abused so as to constitute a public health and social problem warranting the placing of the substance under international control.

On the basis of the limited data available concerning its pharmacological profile and on the fact that it induces physical dependence and that there are very limited reports of actual abuse, the Committee rated the likelihood of abuse of metharbital as moderate. The degree of the public health and social problems associated with the drug was found to be low and its therapeutic usefulness high.

In the light of this assessment, the Committee recommended against scheduling of the drug.

3.16 Methitural

3.16.1 *Substance identification*

Methitural (INN, CAS-467-43-6), chemically 5-(1-methylbutyl)-5-[2-(methylthio)ethyl)]-2-thiobarbituric acid, is also known as methioturiate. It is a racemic mixture.

3.16.2 *Similarity to already scheduled substances*

Methitural has been classified pharmacologically as an ultra-short-acting barbiturate used as an intravenous anaesthetic agent. Barbiturates of this type have not been scheduled. Dose-related drowsiness, vertigo, confusion, and incoordination do occur. The drug, like other barbiturates, is metabolized by hepatic microsomal enzymes and stimulates the production of these enzymes.

3.16.3 *Effects on the central nervous system and mental functions*

Like the other short-acting barbiturates, methitural produces a dose-related depression of the central nervous system, ranging from mild sedation to general anaesthesia and coma. Tolerance, both natural and functional, can occur. Cross-tolerance may occur to other barbiturates, ethanol, and other sedative–hypnotic drugs.

3.16.4 *Dependence potential*

There is no information on the ability of methitural to induce physical or psychic dependence in animals or in man in controlled laboratory studies.

3.16.5 *Actual abuse and/or abuse liability (likelihood of abuse)*

No cases of abuse, seizures, or clandestine production have been reported. It is under national control in five countries.

3.16.6 *Therapeutic usefulness*

Methitural has been used as an intravenous anaesthetic agent. It is produced and/or marketed only in the Federal Republic of Germany. The Committee rated its usefulness as an intravenous anaesthetic agent as high.

3.16.7 *Recommendation*

The Committee found that there was insufficient evidence that methitural is being, or is likely to be, abused so as to constitute a public health and social problem warranting the placing of the substance under international control.

On the basis of the limited data concerning its pharmacological profile, dependence potential, and low actual abuse, the Committee rated the likelihood of abuse of methitural as low. The degree of the public health and social problems associated with the drug was found to be low and its therapeutic usefulness probably high.

In the light of this assessment, the Committee recommended against scheduling of the drug.

3.17 Methohexital sodium

3.17.1 *Substance identification*

Methohexital sodium[1] (CAS-22151-68-4, sodium salt), chemically 5-allyl-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid sodium salt, is also known as methohexitone. It is a racemic mixture.

[1] Modified INN; the INN being methohexital.

3.17.2 *Similarity to already scheduled substances*

Methohexital sodium has been classified pharmacologically as an ultra-short-acting barbiturate used as an intravenous anaesthetic agent. Barbiturates of this type have not been scheduled. Dose-related drowsiness, vertigo, confusion, and incoordination do occur. The drug, like other barbiturates, is metabolized by hepatic microsomal enzymes and stimulates the production of these enzymes.

3.17.3 *Effects on the central nervous system and mental functions*

Like other short-acting barbiturates, methohexital sodium produces a dose-related depression of the central nervous system, ranging from mild sedation to general anaesthesia and coma. Tolerance, both natural and functional can occur. Cross-tolerance may occur to other barbiturates, ethanol, and other sedative–hypnotic drugs.

3.17.4 *Dependence potential*

There are no data on the ability of methohexital to induce physical dependence.

The reinforcing effect of methohexital has been demonstrated in rats and rhesus monkeys by intravenous self-administration experiments, and in baboons by oral self-administration experiments.

3.17.5 *Actual abuse and/or abuse liability (likelihood of abuse)*

Isolated instances of abuse have been reported from Austria, Norway, and the United States of America, but the total number of these cases is very small. No government reported on any public health or social problems caused by this substance. There have been only very minor reports of illicit trafficking and no report of clandestine manufacture. It is under national control in eight countries.

3.17.6 *Therapeutic usefulness*

Methohexital is administered as sodium salt for the induction of general anaesthesia or complete anaesthesia of short duration. The

drug is available in thirty-seven countries mainly for hospital use. The Committee rated the therapeutic usefulness of methohexital as an intravenous anaesthetic agent as high.

3.17.7 *Recommendation*

The Committee found that there was insufficient evidence that methohexital is being, or is likely to be, abused so as to constitute a public health and social problem warranting the placing of the substance under international control.

On the basis of the data concerning its pharmacological profile, dependence potential, and actual abuse, the Committee rated the likelihood of abuse of methohexital sodium as moderate. The degree of the public health and social problems associated with the drug was found to be low and its therapeutic usefulness high.

In the light of this assessment, the Committee recommended against scheduling of the drug.

3.18 Nealbarbital

3.18.1 *Substance identification*

Nealbarbital (INN, CAS-561-83-1), chemically 5-allyl-5-neopentylbarbituric acid, is also known as alneobarbital, nealbarb, nealbarbitone, neallymal, neallymalum.

3.18.2 *Similarity to already scheduled substances*

Nealbarbital has been classified pharmacologically as an intermediate-acting sedative–hypnotic barbiturate with a profile similar to that of pentobarbital. As it is a hypnotic, it is presumed that dose-related drowsiness, vertigo, confusion, and incoordination can occur. The drug, like other barbiturates, is metabolized by hepatic microsomal enzymes and stimulates the production of these enzymes.

3.18.3 *Effects on the central nervous system and mental functions*

The limited data available indicate that the drug produces typical barbiturate-like sedative–hypnotic effects on the central nervous system. As it is a hypnotic, it is presumed that tolerance, both

natural and functional, can occur. Cross-tolerance may occur to other barbiturates, ethanol, and other sedative–hypnotic drugs.

3.18.4 *Dependence potential*

There is no information on the ability of nealbarbital to induce physical or psychic dependence in either animals or man in controlled laboratory studies.

3.18.5 *Actual abuse and/or abuse liability (likelihood of abuse)*

No cases of abuse, seizures, or clandestine production have been reported. It is under national control in five countries.

3.18.6 *Therapeutic usefulness*

Nealbarbital has been used as a sedative and a hypnotic and is presumed to have the same efficacy as other barbiturates in this regard. There is no evidence that the drug has been marketed over the past few years. The Committee rated the therapeutic usefulness of this drug as relatively low.

3.18.7 *Recommendation*

The Committee found that there was insufficient evidence that nealbarbital is being, or is likely to be, abused so as to constitute a public health and social problem warranting the placing of the substance under international control.

On the basis of the very limited data concerning its pharmacological profile, dependence potential, and actual abuse, the Committee rated the likelihood of abuse of nealbarbital as indeterminate. The degree of the public health and social problems associated with the drug was found to be low as was its therapeutic usefulness.

In the light of this assessment the Committee recommended against scheduling of the drug.

3.19 Phenallymal

3.19.1 *Substance identification*

Phenallymal (CAS-115-43-5), chemically 5-allyl-5-phenyl-barbituric acid, is also known as alphenal, phenallymalum, and prophenal. The substance is a racemic mixture.

3.19.2 *Similarity to already scheduled substances*

Information on the general pharmacology of phenallymal is not available. One may assume from its clinical use as a sedative–hypnotic that it may have a profile similar to that of other intermediate-acting barbiturates such as pentobarbital. Its metabolism was studied as one of a series of allyl barbiturates and it did not differ from other members of the series.

3.19.3 *Effects on the central nervous system and mental functions*

There is almost a complete lack of data in animals and man concerning the effects of phenallymal on the central nervous system.

3.19.4 *Dependence potential*

There is no information on the ability of phenallymal to induce physical or psychic dependence in either animals or man in controlled laboratory studies.

3.19.5 *Actual abuse and/or abuse liability (likelihood of abuse)*

There have been no reports on the abuse of phenallymal. The drug is under national control in five countries. There have been no reports of illicit manufacture, illicit trafficking, or seizures of the drug.

3.19.6 *Therapeutic usefulness*

Phenallymal has been recommended as a sedative and hypnotic but no details on its therapeutic usefulness have been found. There is little evidence that the compound is currently being manufactured or sold.

3.19.7 *Recommendation*

The Committee found that there was insufficient evidence that phenallymal is being, or is likely to be, abused so as to constitute a public health and social problem warranting the placing of the substance under international control.

On the basis of the very limited data concerning its pharmacological profile, dependence potential, and actual abuse, the Committee rated the likelihood of abuse of phenallymal as indeterminate. The degree of public health and social problems associated with the drug was found to be low as was its therapeutic usefulness.

In the light of this assessment, the Committee recommended against scheduling of the drug.

3.20 Prazitone

3.20.1 *Substance identification*

Prazitone (INN, CAS-2409-26-9), chemically 5-phenyl-5-(2-piperidylmethyl)-barbituric acid, has no common names. It is a racemic mixture.

3.20.2 *Similarity to already scheduled substances*

No data are available.

3.20.3 *Effects on the central nervous system and mental functions*

No data are available.

3.20.4 *Dependence potential*

No data are available.

3.20.5 *Actual abuse and/or abuse liability (likelihood of abuse)*

There have been no reports of abuse, trafficking, or clandestine manufacture. The drug is under national control in five countries.

3.20.6 *Therapeutic usefulness*

No data are available concerning the therapeutic use of prazitone. There is no evidence that the drug is available for medical use.

3.20.7 *Recommendation*

The Committee found that there was insufficient evidence that prazitone is being, or is likely to be, abused so as to constitute a public health and social problem warranting the placing of the substance under international control.

The Committee rated the likelihood of abuse of prazitone as indeterminate. The degree of the public health and social problems associated with the drug was found to be low as was its therapeutic usefulness.

In the light of this assessment, the Committee recommended against scheduling of the drug.

3.21 Probarbital sodium

3.21.1 *Substance identification*

Probarbital sodium (INN, CAS-143-82-8 sodium salt), chemically 5-ethyl-5-isopropylbarbituric acid, is also known as ethypropymalum (acid). It is a racemic mixture.

3.21.2 *Similarity to already scheduled substances*

Although there are only limited data available, probarbital sodium has been classified pharmacologically as an intermediate-acting sedative–hypnotic barbiturate with a profile similar to that of pentobarbital. As it is a hypnotic, it is presumed that dose-related drowsiness, vertigo, confusion, and incoordination can occur. The drug, like other barbiturates, is metabolized by hepatic microsomal enzymes and stimulates the production of these enzymes.

3.21.3 *Effects on the central nervous system and mental functions*

The drug produces typical barbiturate-like sedative–hypnotic effects on the central nervous system. As it is a hypnotic, it is presumed that tolerance, both natural and functional, can occur. Cross-tolerance may occur to other barbiturates, ethanol, and other sedative–hypnotic drugs.

3.21.4 *Dependence potential*

There is no information on the ability of probarbital sodium to induce physical or psychic dependence in either animals or man in controlled laboratory studies.

3.21.5 *Actual abuse and/or abuse liability (likelihood of abuse)*

There have been no reports of abuse, illicit trafficking, or clandestine manufacture. The drug is under national control in five countries.

3.21.6 *Therapeutic usefulness*

Sodium and calcium salts of the compound have been used as sedatives and hypnotics. Two countries reported that the drug is available for use. There is no indication that the drug has been marketed during the past five years. The Committee rated the therapeutic usefulness of probarbital sodium as relatively low.

3.21.7 *Recommendation*

The Committee found that there was insufficient evidence that probarbital sodium is being, or is likely to be, abused so as to constitute a public health and social problem warranting the placing of the substance under international control.

On the basis of the very limited data concerning its pharmacological profile, dependence potential, and actual abuse, the Committee rated the likelihood of abuse of probarbital sodium as indeterminate. The degree of the public health and social problems associated with the drug was found to be low as was its therapeutic usefulness.

In the light of this assessment, the Committee recommended against scheduling of the drug.

3.22 Propallylonal

3.22.1 *Substance identification*

Propallylonal (CAS-545-93-7, and for the sodium salt CAS-18277-24-2), chemically 5-(2-bromoallyl)-5-isopropylbarbituric acid, is also known as bromoaprobarbital, bromoaprobarbitone, and ibomal.

3.22.2 *Similarity to already scheduled substances*

Propallylonal has been classified pharmacologically as an intermediate-acting sedative–hypnotic barbiturate with a profile similar to that of pentobarbital. As it is a hypnotic, it is presumed that dose-related drowsiness, vertigo, confusion, and incoordination can occur. The drug, like other barbiturates, is metabolized by hepatic microsomal enzymes and stimulates the production of these enzymes.

3.22.3 *Effects on the central nervous system and mental functions*

The drug produces typical barbiturate-like sedative–hypnotic effects on the central nervous system. As it is a hypnotic, it is presumed that tolerance, both natural and functional, can occur. Cross-tolerance may occur to other barbiturates, ethanol, and other sedative–hypnotic drugs.

3.22.4 *Dependence potential*

There is no information on the ability of propallylonal to induce physical or psychic dependence in either animals or man in controlled laboratory studies.

3.22.5 *Actual abuse and/or abuse liability (likelihood of abuse)*

A few cases of abuse and criminal offences associated with propallylonal were reported between 1976 and 1984. No seizures or clandestine manufacture have been reported. It is under national control in six countries.

3.22.6 *Therapeutic usefulness*

Propallylonal is used as a hypnotic and a sedative and has the same efficacy as other barbiturates in this regard. The drug has been reported to be registered and/or available on the market in twelve countries. Over the past two years modest amounts of the drug have been consumed. The Committee rated the therapeutic usefulness of propallylonal as relatively low.

3.22.7 *Recommendation*

The Committee found that there was insufficient evidence that propallylonal is being, or is likely to be, abused so as to constitute

a public health and social problem warranting the placing of the substance under international control.

On the basis of the limited data concerning its pharmacological profile, dependence potential, and actual abuse, the Committee rated the likelihood of abuse of propallylonal as moderate. The degree of the public health and social problems associated with the drug was found to be low as was its therapeutic usefulness.

In the light of this assessment, the Committee recommended against scheduling of the drug.

3.23 Proxibarbal

3.23.1 *Substance identification*

Proxibarbal (INN, CAS-2537-29-3), chemically 5-allyl-5-(2-hydroxypropyl)barbituric acid, is also known as vasalgin. It is a racemic mixture.

3.23.2 *Similarity to already scheduled substances*

The pharmacological profile of proxibarbal differs from that of the classical barbiturates. The hydroxyl side-chain is reported to decrease lipid solubility and abolish hypnotic activity. In human performance tests, proxibarbal did not impair the subjects' ability to discriminate, nor did it prolong the reaction time; also, no effect on the potentiation of the effects of alcohol was demonstrated. It is metabolized to the corresponding lactone, valofane, or alpha-allophanyl-alpha-allyl-gamma-valerolactone. Proxibarbal is not similar to any of the already scheduled substances.

3.23.3 *Effects on the central nervous system and mental functions*

In subchronic, chronic, and toxicological studies, proxibarbal did not reveal any unusual toxicity and was well tolerated. Slight drowsiness or dizziness were the main symptoms observed in some patients. It has no hypnotic effects.

3.23.4 *Dependence potential*

In rhesus monkeys, proxibarbal did not induce physical dependence. Valofane (proxibarbal's transformation product) did

not appear to possess reinforcing properties in rhesus monkeys administering the drug intravenously.

3.23.5 *Actual abuse and/or abuse liability (likelihood of abuse)*

There are no data available on abuse, except for reports of isolated cases of abuse from Austria. It is under national control in six countries.

3.23.6 *Therapeutic usefulness*

Proxibarbal is used for long-term treatment of migraine and other types of vascular headache. It is also recommended in menopausal symptoms, especially for headaches and hot flushes and other premenstrual symptoms.

It is approved for marketing in sixteen countries but is available only in twelve. The volume of production is large. The Committee rated the therapeutic usefulness of proxibarbal as moderate.

3.23.7 *Recommendation*

The Committee found that there was insufficient evidence that proxibarbal is being, or is likely to be, abused so as to constitute a public health and social problem warranting the placing of the substance under international control.

On the basis of the data concerning its pharmacological profile, dependence potential, and actual abuse, the Committee rated the likelihood of abuse of propallylonal as low. The degree of the public health and social problems associated with the drug was also found to be low and its therapeutic usefulness moderate.

In the light of this assessment, the Committee recommended against scheduling of the drug.

3.24 Secbutabarbital

3.24.1 *Substance identification*

Secbutabarbital (INN, CAS-125-40-6, and for the sodium salt CAS-143-81-7), chemically 5-sec-butyl-5-ethylbarbituric acid, is used therapeutically in the form of the sodium salt. Sodium 5-sec-butyl-5-ethylbarbituric acid is also known as butabarbital (sodium), butabarbitone (sodium), and secumalnatrium.

3.24.2 *Similarity to already scheduled substances*

Secbutabarbital has been classified pharmacologically as an intermediate-acting sedative–hypnotic barbiturate with a profile similar to that of pentobarbital. As it is a hypnotic, it is presumed that dose-related drowsiness, vertigo, confusion, and incoordination can occur. The drug, like other barbiturates, is metabolized by hepatic microsomal enzymes and stimulates the production of these enzymes.

3.24.3 *Effects on the central nervous system and mental functions*

The drug produces typical barbiturate-like sedative–hypnotic effects on the central nervous system. As it is a hypnotic, it is presumed that tolerance, both natural and functional, can occur. Cross-tolerance may occur to other barbiturates, ethanol, and other sedative–hypnotic drugs.

3.24.4 *Dependence potential*

There is no information on the ability of secbutabarbital to induce physical dependence in either animals or man in controlled laboratory studies. In one study, rhesus monkeys trained to self-administer thiamylal were given saline to extinguish responding; when responding was extinguished secbutabarbital reinstated responding. This indicates that the drug has reinforcing properties.

3.24.5 *Actual abuse and/or abuse liability (likelihood of abuse)*

Secbutabarbital has been identified in urine samples of street drug users. Three countries reported cases of actual abuse, with one of them reporting only one case, the two others numerous cases. It is under national control in six countries. There have been reports of numerous seizures of legitimately produced substance as well as of trafficking of the formulated product. Cases of forged prescriptions have also been reported. There are no reports of any public health or social problems caused by this substance.

3.24.6 *Therapeutic usefulness*

Secbutabarbital is used as a sedative and hypnotic and has the same efficacy as other barbiturates in this regard. The drug or

combination products containing it have been reported to be registered and/or available on the market in twelve countries. Over the past two years modest amounts of the drug have been consumed. The Committee rated the therapeutic usefulness of secbutabarbital as relatively low.

3.24.7 *Recommendation*

The Committee found that there was sufficient evidence, that secbutabarbital is being, or is likely to be, abused so as to constitute a public health and social problem warranting the placing of the substance under international control in the Convention on Psychotropic Drugs.

On the basis of its pharmacological profile, dependence potential, and evidence of actual abuse, the Committee rated the likelihood of abuse of secbutabarbital as moderate. The degree of the seriousness of the public health and social problems was also found to be moderate and its therapeutic usefulness relatively low.

In the light of this assessment, the Committee recommended that secbutabarbital be placed in Schedule IV.

3.25 Talbutal

3.25.1 *Substance identification*

Talbutal (INN, CAS–115–44–6), chemically 5-allyl-5-sec-butylbarbituric acid, has no common name. It is a racemic mixture.

3.25.2 *Similarity to already scheduled substances*

Talbutal has been classified pharmacologically as an intermediate-acting sedative–hypnotic barbiturate with a profile similar to that of pentobarbital. As it is a hypnotic, it is presumed that dose-related drowsiness, vertigo, confusion, and incoordination can occur. The drug, like other barbiturates, is metabolized by hepatic microsomal enzymes and stimulates the production of these enzymes.

3.25.3 *Effects on the central nervous system and mental functions*

The drug produces typical barbiturate-like sedative and hypnotic effects on the central nervous system. As it is a hypnotic, it is

presumed that tolerance, both natural and functional, can occur. Cross-tolerance may occur to other barbiturates, ethanol, and other sedative-hypnotic drugs.

3.25.4 *Dependence potential*

There is no information on the ability of talbutal to induce physical or psychic dependence in either animals or man in controlled laboratory studies.

3.25.5 *Actual abuse and/or abuse liability (likelihood of abuse)*

There have been sporadic reports on the abuse of talbutal from the United States of America. It is under national control in five countries. There have been reports of seizures and illegal purchases of this substance from the United States of America. There are no reports of clandestine manufacture.

3.25.6 *Therapeutic usefulness*

Talbutal is used as a hypnotic and sedative. At present its use is very limited. The Committee rated the therapeutic usefulness of talbutal as relatively low.

3.25.7 *Recommendation*

The Committee found that there was insufficient evidence that talbutal is being, or is likely to be, abused so as to constitute a public health and social problem warranting the placing of the substance under international control.

On the basis of the data concerning its pharmacological profile, dependence potential, and actual abuse, the Committee rated the likelihood of abuse of talbutal as intermediate. The degree of the public health and social problems associated with the drug was found to be low as was its therapeutic usefulness.

In the light of this assessment, the Committee recommended against scheduling of the drug.

3.26 Thialbarbital

3.26.1 *Substance identification*

Thialbarbital (INN, CAS–467–36–7, and for the sodium salt CAS–3346–29–0), chemically 5-allyl-5-(2-cyclohexen-1-yl)-2-thiobarbituric acid, is also known as thialbarbitone. In medical practice, the sodium salt is used as an anaesthetic. It is a racemic mixture.

3.26.2 *Similarity to already scheduled substances*

Thialbarbital has been classified pharmacologically as an ultra-short-acting barbiturate used as an intravenous anaesthetic agent. Barbiturates of this type have not been scheduled. Dose-related drowsiness, vertigo, confusion, and incoordination do occur. The drug, like other barbiturates, is metabolized by hepatic microsomal enzymes and stimulates the production of these enzymes.

3.26.3 *Effects on the central nervous system and mental functions*

Like the other short-acting barbiturates, thialbarbital produces a dose-related depression of the central nervous system, ranging from mild sedation to general anaesthesia and coma. Tolerance, both natural and functional, can occur. Cross-tolerance may occur to other barbiturates, ethanol, and other sedative–hypnotic drugs.

3.26.4 *Dependence potential*

There is no information on the ability of thialbarbital to induce physical or psychic dependence in controlled laboratory studies.

3.26.5 *Actual abuse and/or abuse liability (likelihood of abuse)*

No actual cases of abuse have been reported and there is no indication that the drug has entered the illicit traffic. It is under national control in five countries.

3.26.6 *Therapeutic usefulness*

Thialbarbital has been recommended and used mainly as an ultra-short-acting intravenous anaesthetic for brief surgical interventions

or as an anaesthetic induction agent. The drug is marketed in only a few countries mainly for hospital use. Veterinary use has also been documented; thialbarbital is regarded to be reliable and economical. The Committee rated the therapeutic usefulness of thialbarbital as an intravenous anaesthetic agent as high.

3.26.7 *Recommendation*

The Committee found that there was insufficient evidence that thialbarbital is being, or is likely to be, abused so as to constitute a public health and social problem warranting the placing of the substance under international control.

On the basis of the data concerning its pharmacological profile, dependence potential, and actual abuse, the Committee rated the likelihood of abuse of thialbarbital as indeterminate. The degree of the public health and social problems associated with the drug was found to be low and its therapeutic usefulness high.

In the light of this assessment, the Committee recommended against scheduling of this drug.

3.27 Thiamylal sodium

3.27.1 *Substance identification*

Thiamylal sodium (CAS–337–47–3), chemically 5-allyl-5-(1-methylbutyl)-2-thiobarbituric acid sodium, is also known as thiaseconal. It is a racemic mixture.

3.27.2 *Similarity to already scheduled substances*

Thiamylal has been classified pharmacologically as an ultra-short-acting barbiturate used as an intravenous anaesthetic agent. Barbiturates of this type have not been scheduled. Dose-related drowsiness, vertigo, confusion, and incoordination do occur. The drug, like other barbiturates, is metabolized by hepatic microsomal enzymes and stimulates the production of these enzymes.

3.27.3 *Effects on the central nervous system and mental functions*

Like the other short-acting barbiturates, thiamylal sodium produces a dose-related depression of the central nervous system,

ranging from mild sedation to general anaesthesia and coma. Tolerance, both natural and functional, can occur. Cross-tolerance may occur to other barbiturates, ethanol, and other sedative–hypnotic drugs.

3.27.4 *Dependence potential*

The substance has been found in one experiment to induce self-administration by the intravenous route in rhesus monkeys with cross-reinforcement to other barbiturates. No information is available on the ability of thiamylal to induce physical dependence in animals or in man.

3.27.5 *Actual abuse and/or abuse liability (likelihood of abuse)*

There are no reports of abuse, and only the United States of America has reported a very small number of seizures. Six countries have reported that the substance is under national control.

3.27.6 *Therapeutic usefulness*

Thiamylal is used as an intravenous anaesthetic. It is available or registered in eight countries mainly for hospital use, although it is used much less extensively than thiopental (see section 3.29). The Committee rated the therapeutic usefulness of thiamylal as an intravenous anaesthetic agent as high.

3.27.7 *Recommendation*

The Committee found that there was insufficient evidence that thiamylal sodium is being, or is likely to be, abused so as to constitute a public health and social problem warranting the placing of the substance under international control.

On the basis of the data concerning its pharmacological profile, dependence potential, and actual abuse, the Committee rated the likelihood of abuse of thiamylal sodium as moderate. The degree of the public health and social problems associated with the drug was found to be low and its therapeutic usefulness high.

In the light of this assessment, the Committee recommended against scheduling of the drug.

3.28 Thiobutabarbital

3.28.1 *Substance identification*

Thiobutabarbital (CAS–2095–57–0, and the sodium salt CAS–947–08–0), 5-(1-methylpropyl)-5-ethyl-2-thiobarbituric acid, is also known as thibutabarbital, and venobarbital. It is a racemic mixture.

3.28.2 *Similarity to already scheduled substances*

Thiobutabarbital has been classified pharmacologically as an ultra-short-acting barbiturate used as an intravenous anaesthetic agent. Barbiturates of this type have not been scheduled. Dose-related drowsiness, vertigo, confusion, and incoordination do occur. The drug, like other barbiturates, is metabolized by hepatic microsomal enzymes and stimulates the production of these enzymes.

3.28.3 *Effects on the central nervous system and mental functions*

Like the other short-acting barbiturates, thiobutabarbital produces a dose-related depression of the central nervous system, ranging from mild sedation to general anaesthesia and coma. Tolerance, both natural and functional, can occur. Cross-tolerance may occur to other barbiturates, ethanol, and other sedative–hypnotic drugs.

3.28.4 *Dependence potential*

There is no information on the ability of thiobutabarbital to induce physical or psychic dependence in either animals or man in controlled laboratory studies.

3.28.5 *Actual abuse and/or abuse liability (likelihood of abuse)*

There are no reports of abuse, seizures, or illicit trafficking. Six countries have reported that the substance is under national control.

3.28.6 *Therapeutic usefulness*

Thiobutabarbital is used as an intravenous anaesthetic. It is available or registered in twelve countries, but is used less extensively

than thiopental (see section 3.29). The Committee rated the therapeutic usefulness of thiobutabarbital as an intravenous anaesthetic agent as high.

3.28.7 *Recommendation*

The Committee found that there was insufficient evidence that thiobutabarbital is being, or is likely to be, abused so as to constitute a public health and social problem warranting the placing of the substance under international control.

Based on the data concerning its pharmacological profile, dependence potential, and actual abuse, the Committee rated the likelihood of abuse of thiobutabarbital as indeterminate. The degree of the public health and social problems associated with the drug was found to be low and its therapeutic usefulness high.

In the light of this assessment, the Committee recommended against scheduling of the drug.

3.29 Thiopental sodium

3.29.1 *Substance identification*

Thiopental sodium (INN, CAS–71–73–8), chemically 5-ethyl-5-(1-methylbutyl)-2-thiobarbituric acid sodium salt, is also known as penthiobarbital, penthiopental sodium, thiomebumal sodium, thiomebumalum, thiomebutal, thiopental, and thiopentone sodium.

3.29.2 *Similarity to already scheduled substances*

Thiopental sodium has been classified pharmacologically as an ultra-short-acting barbiturate used as an intravenous anaesthetic agent. Barbiturates of this type have not been scheduled. Dose-related drowsiness, vertigo, confusion, and incoordination do occur. The drug, like other barbiturates, is metabolized by hepatic microsomal enzymes and stimulates the production of these enzymes.

3.29.3 *Effects on the central nervous system and mental functions*

Like other short-acting barbiturates, thiopental sodium produces a dose-related depression of the central nervous system, ranging

from mild sedation to general anaesthesia and coma. Tolerance, both natural and functional, can occur. Cross-tolerance may occur to other barbiturates, ethanol, and other sedative–hypnotic drugs.

3.29.4 *Dependence potential*

In studies of barbiturate-reinforced responding in animals trained to self-administer the drugs, responding was shown to be increased and was maintained by thiopental sodium, indicating that the drug could potentially cause psychic dependence. There are no reports on the ability of thiopental to induce physical dependence in animals or man.

3.29.5 *Actual abuse and/or abuse liability (likelihood of abuse)*

There are isolated reports of abuse from Austria, Czechoslovakia, and Norway. The substance has occasionally been used for committing suicide. There are a small number of reports of seizures from the Republic of Korea and the United States of America. Nine countries have reported that the substance has been put under national control. No government has reported on any public health or social problems caused by this substance.

3.29.6 *Therapeutic usefulness*

Thiopental is very widely used as an intravenous anaesthetic and to a lesser extent in status epilepticus and in cerebral oedema and cerebral ischaemia. It is available and/or registered in 71 countries, mainly for hospital use. It is effective, and relatively safe to use if administered by skilled health personnel. The Committee rated the therapeutic usefulness of thiopental sodium as an intravenous anaesthetic agent as high.

3.29.7 *Recommendation*

The Committee found that there was insufficient evidence that thiopental sodium is being, or is likely to be, abused so as to constitute a public health and social problem warranting the placing of the substance under international control.

Based on the data concerning its pharmacological profile, dependence potential, and actual abuse, the Committee rated the

likelihood of abuse of thiopental sodium as moderate. The degree of the public health and social problems associated with the drug was found to be low and its therapeutic usefulness high.

In the light of this assessment the Committee recommended against scheduling of the drug.

3.30 Vinbarbital

3.30.1 *Substance identification*

Vinbarbital (INN, CAS–125–42–8), chemically 5-ethyl-5-(1-methyl-1-butenyl)barbituric acid, is also known as butenemalum, vinbarbitalum, and vinbarbitone. It is a racemic mixture.

3.30.2 *Similarity to already scheduled substances*

Vinbarbital has been classified pharmacologically as an intermediate-acting sedative–hypnotic barbiturate with a profile similar to that of pentobarbital. As it is a hypnotic, it is presumed that dose-related drowsiness, vertigo, confusion, and incoordination can occur. The drug, like other barbiturates, is metabolized by hepatic microsomal enzymes and stimulates the production of these enzymes.

3.30.3 *Effects on the central nervous system and mental functions*

The drug produces typical barbiturate-like sedative–hypnotic effects on the central nervous system. As it is a hypnotic, it is presumed that tolerance, both natural and functional, can occur. Cross-tolerance may occur to other barbiturates, ethanol, and other sedative-hypnotic drugs.

3.30.4 *Dependence potential*

There is no information on the ability of vinbarbital to induce physical or psychic dependence in either animals or man in controlled laboratory studies.

3.30.5 *Actual abuse and/or abuse liability (likelihood of abuse)*

Belgium and Finland have reported a few cases of abuse. It has been reported to be found in the illicit market in the Congo, and two

instances of seizures of very small quantities have been reported from the United States of America. The substance is under national control in six countries. No government reported on any public health or social problems caused by this substance.

3.30.6 *Therapeutic usefulness*

Vinbarbital has been used as a daytime sedative and a night-time hypnotic. It has also been used in combination preparations with analgesics, although it has not been established that any improvement in efficacy results. The substance is registered or is available in eight countries, but, as far as could be determined, it is no longer on the market anywhere in the world. The Committee rated the therapeutic usefulness of vinbarbital as relatively low.

3.30.7 *Recommendation*

The Committee found that there was insufficient evidence that vinbarbital is being, or is likely to be, abused so as to constitute a public health and social problem warranting the placing of the substance under international control.

On this basis of the data concerning its pharmacological profile, dependence potential, and actual abuse, the Committee rated the likelihood of abuse of vinbarbital as moderate. The degree of the public health and social problems associated with the drug was also found to be low as was its therapeutic usefulness.

In the light of this assessment, the Committee recommended against scheduling of the drug.

3.31 Vinylbital

3.31.1 *Substance identification*

Vinylbital (INN, CAS–2430–49–1), chemically 5-(1-methylbutyl)-5-vinylbarbituric acid is also known as butyvinal, vinylbarbital, vinylbitone, and vinymalum.

3.31.2 *Similarity to already scheduled substances*

Vinylbital has been classified pharmacologically as an intermediate-acting sedative–hypnotic barbiturate with a profile

similar to that of pentobarbital. As it is a hypnotic, it is presumed that dose-related drowsiness, vertigo, confusion, and incoordination can occur. The drug, like other barbiturates, is metabolized by hepatic microsomal enzymes and stimulates the production of these enzymes.

3.31.3 *Effects on the central nervous system and mental functions*

The drug produces typical barbiturate-like sedative–hypnotic effects on the central nervous system. As it is a hypnotic, it is presumed that tolerance, both natural and functional, can occur. Cross-tolerance may occur to other barbiturates, ethanol, and other sedative–hypnotic drugs.

3.31.4 *Dependence potential*

There is no information on the ability of vinylbital to induce physical or psychic dependence in either animals or man in controlled laboratory studies.

3.31.5 *Actual abuse and/or abuse liability (likelihood of abuse)*

Isolated cases of abuse have been reported from Austria, Belgium, and Finland. However, a somewhat greater number of cases of abuse have been reported from the Federal Republic of Germany. There have been reports of illicit trafficking from the Congo and of seizures from Finland and the United States of America; a number of criminal offences involving vinylbital have been reported from the Federal Republic of Germany. The substance is under national control in four countries.

3.31.6 *Therapeutic usefulness*

Vinylbital is used as a sedative and hypnotic and has the same efficacy as other barbiturates in this regard. The drug has been reported to be registered and/or available on the market in twelve countries. Over the past two years modest amounts of the drug have been consumed. The Committee rated the therapeutic usefulness of vinylbital as relatively low.

3.31.7 *Recommendation*

The Committee found that there was sufficient evidence that vinylbital is being, or is likely to be, abused so as to constitute a public health and social problem warranting the placing of the substance under international control in the Convention on Psychotropic Substances.

On the basis of its pharmacological profile, and on the limited evidence of its dependence potential and evidence of actual abuse, the Committee rated the likelihood of abuse of vinylbital as moderate. The degree of seriousness of the public health and social problems was also found to be intermediate and its therapeutic usefulness relatively low.

In the light of this assessment, the Committee recommended that vinylbital be placed in Schedule IV.

4. RECOMMENDATIONS

The Expert Committee recommended that a number of steps be taken to improve the review process. The specific recommendations are detailed below.

1. The Expert Committee found the model report format suggested by the Third Programme Planning Working Group (PPWG) to be quite useful. However, it had difficulty in separating the available information for inclusion under sections 2 and 3 ("Similarity to already scheduled substances" and "Effects on the central nervous system and mental functions"). It recommended therefore that the PPWG consider combining these sections. In addition, the Expert Committee preferred the term "likelihood of abuse" to "abuse liability" (section 5) and has used this term in this report. The Expert Committee recommended that the PPWG should also adopt this term and better define its components. It would also be useful to consider presenting information on public health and social problems under a separate heading rather than under the section on recommendations.

2. For each drug, a review of data concerning its dependence potential and likelihood of abuse is essential in deciding whether the drug should be placed under control under the Single Convention

on Narcotic Drugs, 1961, and the Convention on Psychotropic Substances, 1971. The Expert Committee recognized the importance of animal data and information from controlled clinical studies in assessing the dependence potential of drugs, and recommended that such data be systematically collected on substances under consideration for control prior to the meeting of the Committee. To assess the likelihood of abuse of a drug, data on the actual abuse of the substance in the population were especially important; the Expert Committee therefore urged that efforts be made to encourage the systematic collection of such data.[1] In addition the Expert Committee urged WHO to request the appropriate national and international agencies to collect such information.

3. The Expert Committee commended the effort of WHO to involve the pharmaceutical industry directly and through the International Federation on Pharmaceutical Manufacturers Associations in the process of collecting information. The Expert Committee recommended that these efforts be continued and expanded, in order to re-emphasize the role of the pharmaceutical industry in preventing and controlling the problems of drug abuse.

4. The Expert Committee recommended that the practice of pre-selection of drugs for review by the Committee, initiated by the Programme Planning Working Group, be continued. The Expert Committee felt that the earlier method of selecting large numbers of substances by chemical or pharmacological class resulted in an in-depth review of too large a number of substances, with the result that the effort as well as the cost involved in such a review were out of proportion in relation to the extent of the public protection achieved.

5. The Expert Committee felt that the problems related to the control of drug abuse could be handled best at the national rather than the international level. The Expert Committee therefore urged WHO and other United Nations agencies involved in the regulation of drugs to help national authorities in their efforts to implement and interpret the Conventions.

The Expert Committee discussed at length the issue of restricted availability of certain useful drugs in developing countries following

[1] Suitable methods for the collection of such data are presented in: WHO Technical Report Series, No. 656, 1981 (*Assessment of public health and social problems associated with the use of psychotropic drugs:* report of a WHO Expert Committee).

the placing of those drugs under international control and as a result of a misinterpretation of the purpose of international control measures. In this regard, the current status of phenobarbital was considered in depth.

Phenobarbital is currently controlled in Schedule IV of The Convention on Psychotropic Substances, 1971. The Committee was informed that, as a result of this control, problems had arisen in a number of developing countries with regard to the use of phenobarbital in the treatment of epilepsy. The incidence of convulsive disorders is high in developing countries and many epileptics are untreated. Phenobarbital is an effective, economical and safe anticonvulsant and is the drug of choice of the health care systems of many developing countries. Moreover, it is included in the WHO list of essential drugs.

In a number of WHO regions, difficulties have been encountered in obtaining phenobarbital for its intended medical use. Pharmacies have become reluctant to stock it because of the extra record-keeping imposed by national authorities or because its inclusion in the Convention has been interpreted as meaning that the substance is dangerous and should be withdrawn from use. This had led to serious problems in the availability of the drug, particularly in rural areas; in primary health care settings, it is often no longer available for prescription by health care workers who are not medically qualified.

The Expert Committee was strongly of the opinion that attention should be given to making clear at the national level the limited extent of restriction required by control in Schedule IV of the Convention on Psychotropic Substances. The Committee stressed the need to explain to all members of national health care teams the real purpose of placing phenobarbital under international control. It is hoped that these measures will lead to easier availability of this important drug. In this regard, the Committee welcomed WHO's collaboration with the International Federation of Pharmaceutical Manufacturers Associations.[1]

Finally, the Committee recommended that WHO should collect evidence from developing countries concerning the scheduling of phenobarbital and any effects this has had on the medical treatment

[1] *Report of the informal consultation on the impact of scheduling psychoactive substances on the practice of medicine and pharmacy*. Unpublished WHO document. MNH/PAD/85/17.

of convulsive disorders. The information collected should be reported to the United Nations Division of Narcotic Drugs and the International Narcotics Control Board with recommendations for possible solutions.